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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,562	12/05/2001	Daniel R. Salomon	302018.3003-100	2653
30407	7590	06/28/2004	EXAMINER	
BOWDITCH & DEWEY, LLP 161 WORCESTER ROAD P.O. BOX 9320 FRAMINGHAM, MA 01701-9320			MOHAMED, ABDEL A	
			ART UNIT	PAPER NUMBER
			1653	

DATE MAILED: 06/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/006,562	Applicant(s) SALOMON ET AL.	
	Examiner Abdel A. Mohamed	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 April 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-36 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>11</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

ACKNOWLEDGMENT TO AMENDMENT, RESPONSE, IDS, STATUS OF THE APPLICATION AND CLAIMS

1. The amendment, remarks and the information disclosure statement (IDS) and Form PTO-1449 filed 4/1/04 are acknowledged, entered and considered. In view of Applicant's request claims 1, 7, 8, 10, 13-15, 19, 20, 22, 25, 26, 28, 29, 31-33 and 35 have been amended. Claims 1-36 are now pending in the application. The objection to the specification and the rejections under 35 U.S.C. 102(b) over the prior art of record are withdrawn in view of Applicant's amendment to the specification and claims and remarks filed 4/1/04. However, the rejection under 35 U.S.C. 103(a) over the prior art of record is maintained.

CLAIMS REJECTION-35 U.S.C. § 103(a)

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

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were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-36 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Nawrocki et al. (Transplantation Proceedings, Vol. 28, No. 6, pp. 3538-3539, 1996) taken with Cramer et al. (Transplantation Proceedings, Vol. 29, page 616, 1997) and Schmid et al. (Eur. Surg. Res., Vol. 30, pp-61-68, 1998).

The reference of Nawrocki et al. discloses like the instantly claimed invention of claims 1, 13, 25, 30-32, 35 and 36 a method and composition thereof for ameliorating or preventing chronic allograft rejection in a mammal by administering a therapeutically effective amount of cyclosporin and 2-chlorodeoxyadenosine (2-CDA), wherein said composition is administered subcutaneously and is efficient to suppress the recipient's B-cell mediated response to the allograft. The reference also discloses a prolongation of cardiac allograft survival in rats (mammals) following combination treatment with 2-CDA and cyclosporin resulting in efficient inhibition of B-cell function including activation, differentiation, and immunoglobulin production as directed to claims 1, 13, 25, 30-32 and 36 (See e.g., pages 3538 and 3539 and Table I).

The reference of Nawrocki et al. differs from claims 1-36 in not teaching the administration of specific dosages and duration time of cyclosporin and 2-CDA and preventing arterial atherosclerosis. However, the secondary reference of Cramer et al.

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discloses a method and composition thereof for ameliorating or preventing chronic allograft rejection including arteriosclerosis in a mammal by administering a therapeutically effective amount of cyclosporin and 2-chlorodeoxyadenosine (2-CDA), wherein the cyclosporin is provided at 5 mg/kg body weight and 2-CDA at 1 mg/kg body weight which overlaps with the claimed ranges of claims 3, 27 and 28. Further, the secondary reference of Schmid et al. discloses a method and composition thereof for ameliorating or preventing chronic allograft rejection in a mammal by administering a therapeutically effective amount of cyclosporin and 2-CDA (See e.g., pages 61-63 and 66-67) as directed to claims 1, 13, 25 and 30-32. The composition is administered orally and the cyclosporin is provided at 10 mg/kg body weight, which overlaps with the claimed ranges of claims 3 and 27 (See e.g., page 61). Furthermore, optimization of dosages and duration of the dosages is within the purview of one of ordinary skill in the art and as admittedly acknowledged on pages 9 and 10 in the instant specification, the selected dosage level depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. Thus, given the teachings of the secondary references and further as acknowledged on page 22, lines 1-2 in the instant disclosure, one skilled in the art will be able to readily adjust the 2-CDA dosage and duration time relation to a human patient's cyclosporin dosage and duration time to obtain the desired therapeutic effect.

Therefore, in view of the above, the combined teachings of the prior art makes obvious a method of ameliorating or preventing chronic allograft rejection including arterial atherosclerosis by administering effective amount of cyclosporin in combination with 2-CDA and a pharmaceutical formulation for administration thereof, absence of sufficient objective factual evidence or unexpected results to the contrary.

ARGUMENTS ARE NOT PERSUASIVE

3. The rejection of claims 1-36 under 35 U.S.C. 103(a) as being unpatentable over Nawrocki et al. (Transplantation Proceedings, Vol. 28, No. 6, pp. 3538-3539, 1996) taken Cramer et al. (Transplantation Proceedings, Vol. 29, page 616, 1997) and Schmid et al. (Eur. Surg. Res., Vol. 30, pp-61-68, 1998).

Applicant's arguments filed 4/1/04 on pages 10-12 of the remarks have been fully considered but they are not persuasive. Contrary to Applicant's arguments, the Examiner has clearly indicated as discussed above under the rejection 103(a) that the primary reference of Nawrocki et al. discloses like the instantly claimed invention of claims 1, 13, 25, 30-32, 35 and 36 a method and composition thereof for ameliorating or preventing chronic allograft rejection in a mammal by administering a therapeutically effective amount of cyclosporin and 2-chlorodeoxyadenosine (2-CDA), wherein said composition is administered subcutaneously and is efficient to suppress the recipient's B-cell mediated response to the allograft. The reference also discloses a prolongation of cardiac allograft survival in rats (mammals) following combination treatment with 2-CDA and cyclosporin resulting in efficient inhibition of B-cell function including

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activation, differentiation, and immunoglobulin production as directed to claims 1, 13, 25, 30-32 and 36 (See e.g., pages 3538 and 3539 and Table I). With respect to Applicant's argument that in Nawrocki et al. study, no histology was performed; no gross pathology or histopathology of the rejected allograft was reported is noted. However, the limitations Applicant argued with (i.e., performing and reporting histology, gross pathology or histopathology of the rejected allograft) are not recited in the rejected claims(s). Nevertheless, the claims are interpreted in light of the specification, limitation from the specification are not read into claims. See *In re Geuns*, 988 F.2nd 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Thus, Applicant's argument is not commensurate to the scope of the claims.

Applicant's assertion that both the Nawrocki et al. reference and Schmid et al. reference report short-term studies of acute, not chronic rejection is noted. However, both reference as discussed above teach the identical composition/formulation and would therefore be expected to have the identical properties and functions. Thus, the burden is on the Applicant to show that the composition/formulation of Schmid et al. reference and Nawrocki et al. reference would not be effective in chronic condition (i.e., in chronic allograft rejection) since the prior art and the instant invention use the same combined composition/formulation (i.e., cyclosporin and 2-chlorodeoxyadenosine) with the same amount of dosages for the same purpose of treatment regardless of its stage (i.e., whether chronic or acute).

In regard to Applicant's arguments that the Cramer et al. reference discloses an amount of drug to be administered per kg, but does not teach or suggest whether that

amount is to be administered once in 90 day period, one or more times a month, one or more times a week or one or more times a day is unpersuasive. Contrary to Applicant's arguments, the secondary reference of Cramer et al. discloses a method and composition thereof for ameliorating or preventing chronic allograft rejection including arteriosclerosis in a mammal by administering a therapeutically effective amount of cyclosporin and 2-chlorodeoxyadenosine (2-CDA), wherein the cyclosporin is provided at 5 mg/kg body weight and 2-CDA at 1 mg/kg body weight which overlaps with the claimed ranges of claims 3, 27 and 28 (See e.g., page 616, under Table 1, Group 3). Similarly, on page 61, the secondary reference of Schmid et al. discloses the administration of a therapeutically effective amount of cyclosporin orally at 10 mg/kg body weights and 2-CDA at 0.1 mg/Kg body weights. Thus, in view of the secondary references dosages which overlaps with the claimed dosages and in view of Applicant's acknowledgement on pages 9 and 10 which states that the selected dosage level depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. It is within the skill of the art to optimize the dosages, route of administration and duration time by starting doses the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. Thus, given the teachings of the secondary references and further as acknowledged on page 22, lines 1-2 in the instant disclosure, one skilled in the art will be able to readily adjust the 2-CDA and cyclosporin dosages, route of administration and duration time relation to a human patient's 2-CDA and

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cyclosporin dosage, route of administration and duration time to obtain the desired therapeutic effect.

Therefore, in view of the above, the combined teachings of the prior art makes obvious a method of ameliorating or preventing chronic allograft rejection including arterial atherosclerosis by administering effective amount of cyclosporin in combination with 2-CDA and a pharmaceutical formulation for administration thereof. Thus, it is made obvious by the combined teachings of the prior art since the instantly claimed invention which falls within the scope of the combined teachings of the prior art method would have been *prima facie* obvious from said prior art disclosure to a person of ordinary skill in the art because as held in host of cases including *Ex parte Harris*, 748 O.G. 586; *In re Rosselete*, 146 USPQ 183; *In re Burgess*, 149 USPQ 355 and as exemplified by *In re Best*, "the test of obviousness is not express suggestion of the claimed invention in any and all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them".

ACTION IS FINAL

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CONCLUSION AND FUTURE CORRESPONDANCE

5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272-0955. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S.F. Low, can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306 for regular communications and (703) 305-7401 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

AM

Mohamed/AAM

June 17, 2004

Christopher S.F. Low
CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
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